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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,326	06/22/2001	George Weiner	C1039/7052 (AWS)	7237

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,326	WEINER ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-15,17-22,24,34,43,56 and 76* is/are pending in the application.

4a) Of the above claim(s) *3,4,22 and 76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7-15,17-21,24,34,43 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4,13,14 attached
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/28/04 has been entered.

2. This Action is in response to the communication filed on 1/28/04. The amendment has been entered. Claims 2 and 6 have been cancelled. Claims 1, 3-5, 7-15, 17-22, 24, 34, 43, 56 and 76 are pending in the application and are addressed herein. Claims 3, 4, 22 and 76 have been withdrawn from consideration for reasons previously set forth. Claims 1, 5, 7-15, 17-21, 24, 34, 43 and 56 are examined herein.

3. Applicant's arguments against the rejections from the previous (Final) action are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 5, 7-15, 17-21, 24, 34 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for:

1) A method for inhibiting the growth of a B-cell malignancy, wherein said B-cell malignancy is a marginal zone lymphoma or B-cell chronic lymphocytic leukemia (B-CLL), said method comprising administering to a subject having the B-cell malignancy:

a) an immunostimulatory nucleic acid sequence that is 6 or more nucleotides in length and comprises an unmethylated CpG motif and a backbone modification, wherein said immunostimulatory nucleic acid is administered in an amount effective to upregulate expression of CD20, CD19 or CD22 in said B-cell malignancy; and

b) an antibody chosen from an anti-CD20 antibody, an anti-CD19 antibody and an anti-CD22 antibody;

wherein administration of the immunostimulatory nucleic acid and the antibody results in the inhibition of the growth of the B-cell malignancy;

2) A method for reducing the growth of a B-cell malignancy wherein said B-cell malignancy is B-CLL or Marginal Zone lymphoma, said method comprising isolating from a subject having said B-cell malignancy a B-CLL or marginal zone lymphoma cell, identifying a surface antigen chosen from CD19, CD20 and CD22, which is not expressed or which is expressed on the surface of the B-CLL or marginal zone lymphoma in an amount lower than that of a normal cell of the same type, and administering to said subject a) an immunostimulatory nucleic acid sequence that is 6 or more nucleotides in length and comprises an unmethylated CpG motif and a backbone modification, wherein said immunostimulatory nucleic acid is

administered in an amount effective to upregulate expression of CD20, CD19 or CD22 in said B-cell malignancy; and

b) an antibody chosen from an anti-CD20 antibody, an anti-CD19 antibody and an anti-CD22 antibody;

wherein the method results in reducing the growth rate of the B-cell malignancy;

3) A method for reducing the growth rate of a B-cell malignancy wherein said B-cell malignancy is B-CLL or Marginal Zone lymphoma, and wherein said B-CLL or said Marginal Zone lymphoma is resistant to antibody therapy; the method comprising administering to a subject having the B-cell malignancy:

a) an immunostimulatory nucleic acid sequence that is 6 or more nucleotides in length and comprises an unmethylated CpG motif and a backbone modification, wherein said immunostimulatory nucleic acid is administered in an amount effective to upregulate expression of CD20, CD19 or CD22 in said B-cell malignancy; and

b) an antibody chosen from an anti-CD20 antibody, an anti-CD19 antibody and an anti-CD22 antibody;

wherein the method results in reducing the growth rate of the B-cell malignancy;

does not reasonably provide enablement for all embodiments embraced by the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Specifically, the specification is not enabling for claims drawn to: 1) **preventing** or completely curing B-cell malignancy in a subject 2) inhibiting the growth of a B-cell malignancy other than B-CLL or marginal zone lymphoma, and 3) upregulating the expression of CD20, CD 19 or CD22 in any cell other than a B-CLL or marginal zone lymphoma cell.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention:

The instant claims are drawn to a method of treating a B-cell malignancy comprising: administering to a subject having, or at risk of developing a B-cell malignancy (a) an immunostimulatory CpG oligonucleotide between 6 and 100 nucleotides long and comprising at least the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated and wherein X_1 X_2 X_3 and X_4 are nucleotides, in an amount effective to upregulate CD20, CD19 or CD 22 expression and b) and an antibody chosen from an anti-CD20 antibody, an anti-CD19 antibody and an anti-CD22 antibody. Certain claims include treating cancer cells that are resistant to antibody therapy. Therefore, the general nature of the invention is cancer immunotherapy and encompasses a administrating a combination of an antibody and an immunostimulatory nucleic acid.

The breadth of the claims:

The breadth of the claims is very broad. For instance the claims encompass treating, preventing or curing any type of B-cell malignancy by administering to an individual who has a B-cell malignancy, or who may not have, but may be at risk of developing a B-cell malignancy: an immunostimulatory nucleic acid that meets the limitations of claim 1, which results in the upregulation of CD20, CD19 or CD22 expression in any cell of the subject, and also administering an anti-CD20, antiCD19, or anti-CD22 antibody.

The unpredictability of the art and the state of the prior art:

Regarding the use immunostimulatory nucleic acids, the art recognizes a number of specific characteristics of the oligonucleotide which are critical for its function as an immunostimulatory molecule. For instance, Krieg (BioDrugs, 1998; 5:341-346) teaches,

> "Synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by 5-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity." (See p. 342, first paragraph).

Similarly, Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches, "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity…" (See p. 114, bottom of second column). Agrawal also teaches that sequences required for CpG related immune stimulation varies from species to species, and indicates, "The optimal motif for recognition by human immune cells is GTCGTT or TTCGTT" (See p. 115, first paragraph). Thus indicating that an oligonucleotide of 6 nucleotides in length can function as an immunostimulatory agent in humans.

Hartmann et al. (J. Immunology, 2000; 164:1617-1624) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in vivo. Specifically, Hartmann teaches, "To have in vivo clinical utility, ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the nonbridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (See p. 1618, first column).

Therefore, in order for an oligonucleotide to stimulate an immune response in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage.

There is no teaching in the prior or post-filing art indicating that any cancer can be prevented or completely cured without a chance of re-occurrence, thus indicating the high degree of unpredictability of curing and preventing cancer. In fact, methods for curing/preventing cancer would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancer cell including preventing genetic mutation, and immortalization.

Working Examples and Guidance in the Specification

The specification has one working example specifically indicating that when mice comprising a B-cell lymphoma (T3C cells), were administered CpG ODN 1826 (a 20mer oligonucleotide with a phosphorothioate backbone (SEQ ID NO: 560) and a mouse IgG2a monoclonal antibody (MS11G6), the mice had a significantly improved survival when compared

to control mice (see Example 3, pages 76-77), thus indicating that the treatment inhibited growth of the B-cell lymphoma. The specification also provides guidance on constructing an immunostimulatory oligonucleotide comprising at least one unmethylated CpG dinucleotide. The specification also indicates a general formula for the immunostimulatory oligonucleotide. It is disclosed that the CpG nucleic acid is represented by <u>at least</u> the formula (emphasis added):

5' $N_1X_1CGX_2N_2$ 3'

wherein X_1 and X_2 are nucleotides and N is any nucleotide and N_1 and N_2 are nucleic sequences composed of from about 0-25 N's each (see p. 38 of the specification).

It is noted that there are no examples or guidance indicating anything other than an immunostimulatory nucleic acid comprising an unmethylated CpG motif can be used to upregulate CD19 or CD20 expression. Also, there are no examples or guidance disclosing the method as useful for treating any kind of cancer other than B-CLL and marginal zone lymphoma, and there is no example/guidance indicating that B-cell malignancy can be prevented.

The data presented in the specification also clearly indicates that the unmethylated CpG oligonucleotides upregulated expression of CD20 and CD19 in **<u>ONLY</u>** B-CLL cells and Marginal Zone Lymphoma cells (but not in any other B-cell malignancies such as: Large cell lymphoma, mantle cell lymphoma, diffuse mixed lymphoma or reactive follicular hyperplasia; e.g., see Figue 3). There is no indication in the specification, or in the prior art that the immunostimulatory oligonucleotides can upregulate CD20, CD19 or CD22 expression in any other cells than B-CLL or marginal zone lymphoma cells.

<u>Quantity of Experimentation</u>

Considering the breadth of the claims and the limited working examples and guidance in the specification, one of skill in the art would be required to perform additional experimentation in order to be able to effectively use the invention to the full scope of the claims. For instance, considering the prior art teachings and the examples/guidance provided in the specification, one of skill in the art could use the method for inhibiting growth of a B-CLL or marginal zone lymphoma tumors provided the nucleic acid comprises an oligonucleotide comprising at least one unmethylated CpG motif, at least 6 nucleotides in length, and has a modified backbone, to protect the oligonucleotide from degradation—several examples of backbone modification are well known in the art, such as phosphorothioate modification, 2-O-Me modification, etc. However, additional experimentation would be required in order to use any nucleic acid that does not specifically have these characteristics to treat or prevent any type B-cell malignancy. For instance, one would have to show how a nucleic acid comprising an unmethylated CpG motif, but without backbone modification could function as an immunostimulatory molecule. Considering the teaching in the art that it is imperative for the oligonucleotide to have a modified backbone in order to protect the oligonucleotide from degradation by nucleases. Also, considering that the claims encompass upregulating CD20, CD19 and CD22, but does not specifically indicate in which cells the antigens are upregulated, additional experimentation would be required in order to show that upregulating CD20, CD19 and CD22 expression in cells other than the B-CLL and marginal zone lymphomas would result in an effective treatment. Considering that the specification also clearly indicates that the oligonucleotides only upregulate CD19 and CD20 expression in B-CLL and Marginal Zone lymphoma cells and explicitly indicates that the oligonucleotides DO NOT upregulate CD20 expression in other B-cell

malignancies, additional experimentation would have to be done to be able to use the method to upregulate CD20, CD19 and CD22 expression in, and also to treat any B-cell malignancy other than B-CLL or Marginal Zone lymphoma.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering 1) the high degree of unpredictability of recognized in the art indicated above; 2) the breadth of the claims; 3) the limited working examples and guidance in the specification; and 4) the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed to the full scope encompassed by the claims is undue.

Response to Arguments

6. Applicant's arguments filed 1/28/04 have been fully considered but they are not persuasive.

7. Applicants have amended the base claim (claim 1) such that the claim is now drawn to a method for treating a B-cell malignancy comprising administering to a subject at risk of developing a B-cell malignancy (a) an CpG oligonucleotide (as indicated in claim 1) in an effective amount to upregulate CD20 expression and (b) an anti-CD20 antibody. Applicants argue that they have deleted the "preventing" language, thus overcoming the rejection as it pertains to "preventing cancer". In response, it is respectfully pointed out that amended claim 1 still encompasses "treating" a person "at risk of developing a B-cell malignancy"—which

encompasses "treating" a person who does not yet have cancer, as well as completely curing cancer and preventing any relapse. Furthermore, the specification clearly states, "With respect to the prophylactic treatment methods, the invention is aimed at administering the compositions of the invention to a subject at risk of developing cancer." (See p. 17, lines 3-4 of the specification). Considering that the specification clearly contemplates "prophylactic treatment" of a "subject at risk of developing cancer", the instant claims are interpreted as encompassing a method for preventing cancer.

8. With respect to the notion that the oligonucleotide must be protected from degradation,

Applicants argue,

> "[the] claims should not be limited to phosphorothioate oligonucleotides, as suggested by the Examiner at page 9 of the Office Action, because the specification at pages 41-43 discloses a number of approaches and structures, including but not limited to phosphorothioate modification, that can be used to produce stabilized oligonucleotides. Further, the teaching of Hartmann et al., relied upon by the Examiner for the proposition that the immunostimulatory nucleic acid must be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage, discloses only the use of 'bare' nucleotides in aqueous solution and does not take into account effects of formulation or dose. For example, page 68, line 22 - page 69, line 3 of the specification discloses, inter alia, nucleic acids formulated as nucleic acid delivery complexes, including, for example, nucleic acids encapsulated by liposomes. Furthermore, pharmacokinetic considerations can be overcome by use of increased doses."

With respect to applicants arguments that the claims should not be specifically limited to phosphorothioate modified oligonucleotides, it is acknowledged that there are a number of well known backbone modification which can be done to protect the oligonucleotide from nuclease degradation. However, the only known modifications, as indicated by Hartmann, are backbone modifications. There is no indication in the prior art that anything other than backbone modification would protect the oligonucleotides from degradation AND result in the desired

effect— immunostimulation and, in this case, upregulation of a tumor antigen in the tumor cells. Applicants' arguments that delivery complexes (such as liposomes) or pharmacokinetic consideration can overcome this problem is not acceptable as it is considered only an opinion, without data supporting the opinion. Applicants are respectfully reminded that First, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Here, the Applicants' statements that delivery complexes such as liposomes or pharmacokinetic considerations an overcome the problems taught in the prior art must be supported by evidence, not argument.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 5, 7, 10, 12-14, 17-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration").

Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of CD20 because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification). Furthermore, the oligonucleotide would not hybridize to genomic DNA or RNA under stringent conditions.

Wooldridge does not specifically teach that the method can utilize an anti-CD20 antibody, that the CD20 antibody used is specifically C28B, the nucleic acid used would not hybridize with genomic DNA or RNA under stringent conditions, that that the oligonucleotide is bacterial DNA, or that the oligonucleotide and antibody can be administered together.

Taji teaches that anti-CD20 antibodies (specifically, C2B8 antibodies), can be used to inhibit the growth of CD20 positive B-cell lymphoma cells (Specifically, SU-DHL-4 and SU-DHL-6 cells) which express a low level of CD20. Taji teaches that the C2B8 antibodies induce apoptosis in the lymphoma cells which may account for the effectiveness of the C2B8 antibody therapy. (e.g., see abstract, etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Taji in order to make a method for inhibiting the growth of B-cell lymphoma cells in a subject having SU-DHL-4 or SU-DHL-6 lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the C2B8 antibody taught by Taji, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted

in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Furthermore, it would have been prima facie obvious to perform routine optimization to use a bacterial DNA oligonucleotide comprising the unmethylated CpG since Wooldridge teaches that bacterial DNAs comprising the unmethylated CpG motif are immunostimulatory (e.g., see p. 2994, first column); and it would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the selection of the source of the nucleic acid, or that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

12. Claims 1, 5, 7, 8, 10-14, 17-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Winkler et al. (Blood 1999; 94(7), pages 2217-2224).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a

phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of CD20 because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification). Furthermore, the oligonucleotide would not hybridize to genomic DNA or RNA under stringent conditions.

Wooldridge does not specifically teach that the method can utilize an anti-CD20 antibody, that the CD20 antibody used is specifically C2B8 or Rituximab, that the nucleic acid used would not hybridize with genomic DNA or RNA under stringent conditions, that that the oligonucleotide is bacterial DNA, or that the oligonucleotide and antibody can be administered together.

Winkler teaches that anti-CD20 antibodies (specifically, Rituximab, which is also referred to as "IDEC C2B8"), can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Winkler in order to make a method for inhibiting the growth of B-CLL lymphoma cells in a subject having B-CLL lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the Rituximab (IDEC C2B8) antibody taught by Winkler, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

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> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is

> not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the selection of the source of the nucleic acid, or that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

13. Claims 1, 5, 7, 9, 10, 12-14, 17-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756 and further in view of Pawade et al. (Histopathology, 1995; 27(2) pages 129-137)..

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed

in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of CD20 because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification). Furthermore, the oligonucleotide would not hybridize to genomic DNA or RNA under stringent conditions.

Wooldridge does not specifically teach that the method can be used to treat Marginal Zone Lymphoma cells using an anti-CD20 antibody, or that the CD20 antibody used is specifically C28B, or that that the oligonucleotide is bacterial DNA, or that the oligonucleotide and antibody can be administered together.

Taji teaches that anti-CD20 antibodies (specifically, C2B8 antibodies), can be used to inhibit the growth of CD20 positive B-cell lymphoma cells (Specifically, SU-DHL-4 and SU-DHL-6 cells) which express a low level of CD20. Taji teaches that the C2B8 antibodies induce apoptosis in the lymphoma cells which may account for the effectiveness of the C2B8 antibody therapy. (e.g., see abstract, etc.)

Pawade teaches that marginal zone lymphoma cells are CD20 positive, indicating that marginal zone lymphoma cells express CD20 antigen.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Taji in order to make a method for inhibiting the growth of marginal zone lymphoma cells in a subject having marginal zone lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in

combination with the C2B8 antibody taught by Taji, with a reasonable expectation of success. Since Pawade teaches marginal zone lymphoma cells express CD20 antigen, and since Taji teaches that an anti-CD20 antibody (C2B8) can be used to treat CD20-expressing lymphocytes, there is a reasonable expectation of success

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Furthermore, it would have been prima facie obvious to perform routine optimization to use a bacterial DNA oligonucleotide comprising the unmethylated CpG since Wooldridge teaches that bacterial DNAs comprising the unmethylated CpG motif are immunostimulatory (e.g., see p. 2994, first column); and it would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the selection of the source of the nucleic acid, or that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

14. Claims 1, 5, 7, 9, 10, 12-14, 17-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756 and further in view of US Patent 5,969,135 (Ramasamy et al.).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of CD20 because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the

specification). Furthermore, the oligonucleotide would not hybridize to genomic DNA or RNA under stringent conditions.

Wooldridge does not specifically teach that the method can be used to B-cell lymphoma cells using an anti-CD20 antibody, or that the CD20 antibody used is specifically C28B,or that the oligonucleotide comprises an amino acid backbone modification, or that that the oligonucleotide is bacterial DNA, or that the oligonucleotide and antibody can be administered together.

Taji teaches that anti-CD20 antibodies (specifically, C2B8 antibodies), can be used to inhibit the growth of CD20 positive B-cell lymphoma cells (Specifically, SU-DHL-4 and SU-DHL-6 cells) which express a low level of CD20. Taji teaches that the C2B8 antibodies induce apoptosis in the lymphoma cells which may account for the effectiveness of the C2B8 antibody therapy. (e.g., see abstract, etc.)

Ramasamy teaches backbone modifications which can be made on therapeutic oligonucleotides in order to improve certain properties of the oligonucleotide, including increasing their stability towards enzymes. Ramasamy teaches that an amino acid residue modification to the backbone of the oligonucleotide is one such modification (e.g., see column 1, lines 35-60; and column 3, lines 33-45, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Taji in order to make a method for inhibiting the growth of B-cell lymphoma cells in a subject having B-cell lymphoma cells, comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the C2B8 antibody taught by Taji, wherein the oligonucleotide comprises an amino acid

modified backbone, with a reasonable expectation of success. Since Ramasamy teaches that the amino acid backbone modification decreases degradation of the oligonucleotide in vivo, there is a reasonable expectation of success

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Furthermore, it would have been prima facie obvious to perform routine optimization to use a bacterial DNA oligonucleotide comprising the unmethylated CpG since Wooldridge teaches that bacterial DNAs comprising the unmethylated CpG motif are immunostimulatory (e.g., see p. 2994, first column); and it would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the selection of the source of the nucleic acid, or that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

15. Claims 24, 34 and 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD22 antibodies, as well as anti-CD19 antibodies. (e.g., see abstract, etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19 or CD22 antibodies taught by Goldenberg, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to first isolate a B-cell from the patient and identify the level of the antigens CD19, CD20 or CD22 compared to normal cells before administering the therapeutic composition to the subject. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the determining the level of CD19, CD20 or CD22 antigens was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

16. Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of US Patent 5,208,146 (Irie).

Wooldridge teaches a method of inhibiting the growth of a cancer (B-cell malignancy) wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995,

first column and Figure 1) was administered (300ug) to mice comprising the cancer. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach the method can be used to treat cancer using an IgG1 isotype antibody.

Irie teaches a method of inhibiting the growth of tumors (such as human melanomas) by administering an IgG1 isotype antibody to a subject comprising a tumor that expresses an antigen (recognized by the IgG1 isotype antibody (e.g., see abstract; column 3 lines 19-25)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Irie in order to make a method for inhibiting the growth of tumor cells in a subject having the tumor cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the IgG1 isotype antibodies taught by Irie, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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